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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/008,789

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C. Frank Bennett

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02/23/2004

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EXAMINER

GIBBS, TERRA C

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 02/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/008,789

Applicant(s)

BENNETT ET AL.

Examiner

Terra C. Gibbs

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 23 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,2,4-10,12-15 and 19-22 is/are pending in the application.
- 4a) Of the above claim(s) 21 and 22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-10,12-15,19 and 20 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other:

### **DETAILED ACTION**

It is noted that a Notice of Non-Responsive Amendment was filed on November 17, 2003 in the instant Application. In a conversation with Susan Hubl, on or around December 15, 2003, it became apparent that the Notice of Non-Responsive Amendment filed on November 17, 2003 was issued by the Examiner in error because the Notice states that the pending claims are drawn to a different invention than the originally presented invention. However, an Office Action was filed on May 21, 2003 regarding said pending claims. The Examiner informed Ms. Hubl that the Action filed November 17, 2003 would be withdrawn in view of this error, and a new Office Action would be made of record.

This Office Action is a response to the Amendment filed September 23, 2003 in Paper No. 12.

Claims 3, 11 and 16-18 were previously canceled. Claims 1 and 20 have been amended. New claims 21 and 22 are acknowledged.

Claims 21 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a different invention than originally presented (see Response to Remarks below).

Claims 1, 2, 4-10, 12-15, and 19-22 are pending in the instant application.

Claims 1, 2, 4-10, 12-15, 19, and 20 have been examined on the merits.

*Response to Remarks*

Applicant's Notice of Acceptance of Power of Attorney, filed May 29, 2003 in Paper No. 10 is acknowledged.

Applicants have reinstated cancelled claim 3 as new claim 21 and added new claim 22. Claims 21 and 22 are drawn to approximately 49 unique nucleotide antisense sequences targeted to different and specific regions of a nucleic acid encoding thyroid hormone receptor interactor 6 (SEQ ID NO:3). Applicants contend that in the event the Examiner decides to issue a restriction requirement, Applicants will **elect the species** of SEQ ID NO:22. Applicants further contend that claims 1 and 2 are linking claims, linking the 49 unique nucleotide antisense sequences targeted to different and specific regions of a nucleic acid encoding thyroid hormone receptor interactor 6. Applicants contend that if claims 1 and 2 are allowable, all the unique nucleotide antisense sequences targeted to different and specific regions of a nucleic acid encoding thyroid hormone receptor interactor 6 will be subject to examination. Applicants also contend that claim 21, listing 49 unique nucleotide antisense sequences targeted to different and specific regions of a nucleic acid encoding thyroid hormone receptor interactor 6, should be a species election because the 49 unique nucleotide antisense sequences targeted to different and specific regions of a nucleic acid encoding thyroid hormone receptor interactor 6 are related in that each species is a compound that both hybridizes to and inhibits the expression of TRIP6. Applicant argue that the species set forth in claim 21 (particular oligonucleotide sequences) falls within the genus of claim 1 (compounds targeted to a nucleic acid encoding Trip6) and the subgenus of claim 2 (antisense oligonucleotide compounds targeted to a nucleic acid encoding Trip6).

It is noted that on August 27, 2002, the Attorney of Record, Jane Licata, canceled claim 3 and amended claim 1 to incorporate the target sequence of SEQ ID NO:3, after a telephone interview with the Examiner. Therefore, Applicant has amended the claims to read on compounds targeted to SEQ ID NO:3, and, in essence, elected SEQ ID NO:3 by original presentation. New claims 21 and 22, drawn to unique nucleotide antisense sequences targeted to different and specific regions of SEQ ID NO:3, would require a separate and distinct search from that of the originally presented claims to compounds targeted to SEQ ID NO:3. A new separate and distinct search would be required for each of these sequences, separate from the search of SEQ ID NO:3. Applicants have received an action on the merits for the originally presented invention, compounds targeted to SEQ ID NO:3 and claims 21 and 22 are drawn to a different invention than originally presented and are thereby withdrawn from further consideration.

In response to Applicants arguments, Applicants are correct in contending that claims 21 and 22 would be subject to a restriction requirement. Applicants are incorrect in contending that an **election of species**, not **restriction** should be required among the unique nucleotide antisense sequences listed in claims 21 and 22. The unique nucleotide antisense sequences listed in claims 21 and 22 are distinct inventions. Although the antisense compounds claimed each targets the expression of the same gene, the compound targeting the recited target region sequences are considered to be unrelated, since each region claimed is structurally and functionally independent and distinct for the following reasons: Each region has a unique nucleotide sequence corresponding to the recited target region, each region targets a different and specific location of the nucleic acid thyroid hormone receptor interactor 6 (SEQ ID NO:3) and each region, upon binding of antisense to the nucleic acid encoding human breast cancer-1

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functionally modulates (increases or decreases) the expression of the gene and to varying degree (per applicants' Table 1 in the specification). Therefore, Applicants contention that the species set forth in claim 21 falls within the genus of claim 1 and the subgenus of claim 2 is incorrect. Instead the unique nucleotide antisense sequences listed in claims 21 and 22 are each unrelated, independent, and distinct inventions.

In summary, claims 21 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a different invention than originally presented.

#### ***Claim Objections***

Claims 1, 2, 4-10, 12-15, 19 and 20 were objected to for informalities(s). **This objection is withdrawn** in view of Applicants Amendment to the claim 1 to replace "a" with "the".

#### ***Claim Rejections - 35 USC § 112***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4-10, 12-15, 19 and 20 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn against claims 1, 2, 4-10, 12-15, and 20 but maintained against claim 19**, in view of Applicants arguments, filed September 23, 2003 in Paper No. 12.

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***Claim Rejections - 35 USC § 103***

Claims 1, 2, 4-10, and 12-14 were rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider (Forschungszentrum Karlsruhe, 2001, FZKA 6587, 1-139) in further view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288). **This rejection is withdrawn** in view of the fact that the Examiner discovered that the Schneider reference became available in the commercial database, CAPLUS, on November 19, 2001, several days after the filing of the instant application and is therefore not prior art.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Claims 1, 12, 19, and 20 are rejected under 35 U.S.C. 102(b) or 35 USC 103(a) as being anticipated by or obvious over Murthy et al (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667). **This is a new rejection.**

Murthy et al. disclose an oligonucleotide primer of the following sequence: 5'-CTGGAAGTGAAGACCCAGCAGGTA-3' (ZRP-R8), see page 20680, last paragraph. This oligonucleotide primer is reverse complementary to nucleobases 1628-1603 of SEQ ID NO:3 of the instant invention. Since the oligonucleotide primer of Murthy et al. meets all the structural requirements of the instant claims, the oligonucleotide primer would also be expected to specifically hybridize to a nucleic acid encoding thyroid hormone receptor interactor 6, as per applicant's definition set forth in the specification as filed, pages 8 and 9, lines 12-37 and 1-8, respectively.

Furthermore, since the prior art oligonucleotide primers meets all the structural limitations of the claims, the prior art oligonucleotide primer would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of

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function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims."

Therefore, the instant invention is anticipated or obvious over Murthy et al.

Claims 1, 2, 19, and 20 are rejected under 35 U.S.C. 103(a) as being obvious over Murthy et al. (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667) in view of Milligan et al. (Journal of Medicinal Chemistry, 1993 Vol. 36:1923-1937). **This is a new rejection.**

Claims 1, 2, 19, and 20 are drawn to a compound 8 to 50 nucleobases in length targeted to the 5'-untranslated region, the start codon region, the coding region, or the 3'-untranslated region of a nucleic acid molecule encoding thyroid hormone receptor interactor 6 (SEQ ID NO:3); wherein said compound specifically hybridizes with said nucleic acid molecule encoding thyroid hormone receptor interactor 6 and inhibits the expression of thyroid hormone receptor interactor 6; and wherein the compound is an antisense.

Murthy et al. teach the cDNA cloning of human ZRP-1 (also called thyroid hormone receptor interactor 6), see Figure 1. Murthy et al. also identify the structural domains of ZRP-1, including the 5'-untranslated region, the start codon region, the coding region, or the 3'-untranslated region, and the region(s) involved in protein-protein interactions. Murthy et al. also teach that the identification of other protein interacting domains is required for a better understanding of the role of ZRP-1 in cellular function.

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Milligan et al. teach antisense techniques as a tool for probing the functions of individual genes. Milligan et al. further teach making an antisense oligonucleotide if the mRNA sequence (or cDNA) is known:

Antisense oligodeoxynucleotides (ODNs) have been proposed as a major class of new pharmaceuticals. In general, antisense refers to the use of small, synthetic oligonucleotides, resembling single-stranded DNA, to inhibit gene expression [references omitted]. Gene expression is inhibited through hybridization to coding (sense) sequences in a specific messenger RNA (mRNA) target by Watson-Crick base pairing in which adenosine and thymidine or guanosine and cytidine interact through hydrogen bonding (Figure 1). These simple base-pairing rules govern the interaction between the antisense ODNs and the cellular RNA, allowing the design of ODNs to target any gene of a known sequence (see Milligan et al., at p. 1923).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to make antisense nucleic acids targeting thyroid hormone receptor interactor 6 by using the ZRP-1 sequence taught by Murthy et al. and following the method of Milligan et al. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make antisense nucleic acids targeting thyroid hormone receptor interactor 6 and inhibit the expression of thyroid hormone receptor interactor 6 in cells since Yi et al. (Genomics, 1998 Vol. 49:314-316) have taught that thyroid hormone receptor interactor 6 plays a role in myeloid diseases and uterine lymphoma.

It is noted that there is no evidence of record to show any such differences between the ZRP-1 sequence of Murthy et al. and SEQ ID NO:3 of the instant invention that would have resulted in an artisan not being able to successfully design and use antisense oligonucleotides targeted to different sites/regions of thyroid hormone receptor interactor 6 of SEQ ID NO:3 of the instant invention.

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The invention as a whole would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 4-10 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murthy et al. (Journal of Biological Chemistry, 1999 Vol. 274:20679-20667) in view of Milligan et al. (Journal of Medicinal Chemistry, 1993 Vol. 36:1923-1937) as applied to claims 1 and 2 above, and further in view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288). **This is a new rejection.**

Claims 4-10 and 12-15 are draw to a compound 8 to 50 nucleobases in length targeted to the 5'-untranslated region, the start codon region, the coding region, or the 3'-untranslated region of a nucleic acid molecule encoding thyroid hormone receptor interactor 6 (SEQ ID NO:3); wherein said compound specifically hybridizes with said nucleic acid molecule encoding thyroid hormone receptor interactor 6 and inhibits the expression of thyroid hormone receptor interactor 6, wherein the antisense oligonucleotides comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding thyroid hormone receptor interactor 6 and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

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Murthy et al. and Milligan et al. are relied upon as cited in the 35 U.S.C 103(a) rejection against claims 1, 2, 19, and 20.

Murthy et al. and Milligan et al. do not teach antisense oligonucleotides comprising at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising a nucleic acid molecule encoding thyroid hormone receptor interactor 6 and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Baracchini et al. teach antisense oligonucleotide compounds of 8 to 50 nucleobases in length can be synthesized to a preferred gene of interest to modulate gene expression (see column 8, lines 57-62). It is also well known in the art that an antisense oligonucleotide of 8 to 50 nucleobases in length is a conventional size range for optimal binding of a gene of interest. Baracchini et al. also teach the synthesis and use of antisense oligonucleotides targeted to preferred target regions such as the 5'-untranslated region, the start codon region, the coding region, or the 3'-untranslated region (see column 9, lines 6-67 and column 10, lines 1-25). Baracchini et al. further teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Baracchini et al. further teach antisense oligonucleotides with phosphorothioate-modified backbones (see column

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6, line 37)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties (see Table I)... with modified nucleobases, such as 5-methylcytosine (see column 7, lines 15-25). Baracchini et al. finally teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 8, lines 12-19).

Fritz et al. teach a composition comprising an antisense oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. Fritz et al. further teach that oligonucleotides, in combination with steric stabilizers, exhibit high colloidal stability with low toxic side effects as required for biological experiments in cell culture and *in vivo* (see page 287, last paragraph).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to make antisense nucleic acids targeting thyroid hormone receptor interactor 6 by using the ZRP-1 sequence taught by Murthy et al. and following the method of Milligan et al. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make antisense nucleic acids targeting thyroid hormone receptor interactor 6 and inhibit the expression of thyroid hormone receptor interactor 6 in cells since Yi et al. have taught that thyroid hormone receptor interactor 6 plays a role in myeloid diseases and uterine lymphoma. One of ordinary skill in the art would have been motivated to make a compound 8 to 50 nucleobases in length targeted to the 5'-untranslated region, the start codon region, the coding region, or the 3'-untranslated region of a nucleic acid molecule encoding thyroid hormone receptor interactor 6 (SEQ ID NO:3) since Baracchini et al. taught antisense oligonucleotides 8 to 50 nucleobases in length can optimally modulate gene expression and because it is well known in the art to target different sites within a gene for the oligonucleotide

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interaction to occur such that desired effect, e.g., detection or modulation of expression of the protein, will result. One of ordinary skill in the art would have been motivated and expected success in making antisense nucleic acids targeting thyroid hormone receptor interactor 6 by using the ZRP-1 sequence taught by Murthy et al. and following the method of Milligan et al. with various modifications and substitutions following the methods of Baracchini et al. and Fritz et al. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to modify the antisense oligonucleotides since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal stability with low toxic side effects as required for biological experiments (see Baracchini et al., column 3, lines 17-41, column 6, line 37 and Table I and Fritz et al. page 287, last paragraph).

The invention as a whole would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

### ***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The Examiner can normally be reached on M-F 9:00-5:00.

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If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg

February 10, 2004

  
KAREN A. LACOURCIERE, PH.D  
PRIMARY EXAMINER